

**REMARKS**

Claims 82-93 are all the claims pending in the application; claims 82 and 84 have been allowed; claims 83 and 85-93 are rejected.

After entry of this amendment, claims 92 and 93 will be cancelled, claim 94 will be added, and claims 82-91 and 94 will be pending.

Support for homologues that induce a protective immune response (as recited in claims 83, 85 and 94) may be found at page 33, line 29, through page 34, lines 29-31.

New claim 94 combines the subject matter of claim 86 (and the claims from which claim 86 depends) and claim 93. Further support for claim 94 may be found at page 32 of the specification.

No new matter has been added. Entry of the amendment is respectfully requested.

**I. General Comments on Subject Matter of Amended Claims**

In the Office Action dated October 21, 2003, the Examiner expresses concern that several of the claims read on a combination of a substantially pure CsaE polypeptide, in combination with a substantially pure CsaB polypeptide or the CS4 antigen. The Examiner notes that Applicants indicated in the Response filed August 7, 2003, that the “substantially pure” language in the claims was intended to exclude the combination of the CsaE antigen with the CsaB antigen, which, together, dimerize to form the CS4 antigen. The Examiner concludes that as the “substantially pure” language excludes the presence of other ETEC antigens, claims indicating the presence of such other antigens are improper and inconsistent with the “substantially pure” language.

In explanation, Applicants first confirm that in view of the “substantially pure” language used in each of the independent claims, substantially pure CsaE is CsaE that exists in an unassociated state. Thus, in each embodiment of the claims, there is at least some CsaE present that is not in the form of an oligomer with any other polypeptide encoded by the *csa* operon.

It is important to note that merely combining CsaE and CsaB will not result in the spontaneous formation of the CS4 antigen, or any oligomer for that matter. While the CS4 fimbria is comprised of CsaE and CsaB, these two elements only associate through the actions of the CsaA chaperone-like protein. Thus, a combination of CsaE and CsaB alone would not result in the production of the CS4 fimbria, i.e., CsaE and CsaB do not spontaneously oligomerize. Nor would a combination of CsaE, CsaB and the CS4 antigen result in the formation of more CS4 antigen. Again, the presence of CsaA is required. Please see the enclosed Declaration Under 37 C.F.R. §1.132 for more comments in this regard.

Thus, “substantially pure CsaE,” in a composition also consisting essentially of CsaB and the CS4 antigen (as recited in claim 94), will remain “substantially pure.” That is, neither CsaE and the CS4 antigen, nor CsaE, CsaB and the CS4 antigen will autonomously form an independent biological complex. CsaB and the CS4 antigen are merely additional proteins that may be included in the composition.

The Examiner’s attention is further drawn to claims 86 and 94. These two claims are similar in that both recite immunogenic compositions consisting essentially of substantially pure CsaE and other components. In the case of claim 86, the other components include, e.g., a “carrier or diluent.” In claim 94, the other components include the polypeptide CsaB and/or the

CS4 antigen. In both claims 86 and 94, CsaE continues to exist in a substantially pure form. As discussed above, CsaE does not oligomerize with CsaB or the CS4 antigen.

Applicants further note that claims 86 and 94 have been amended to use the transitional phrase “consisting essentially of.” Thus, components that would materially effect the immunogenic composition, e.g., CsaA and CsaC, are not included in the claims. No additional components are encompassed in the claims that could alter the basic and novel characteristics of CsaE. As a result, components that might lead to the oligomerization of CsaE with another protein are excluded from the claim (as a heteroligomer containing CsaE would likely have “altered” basic and novel characteristics compared to CsaE alone).

## **II. Claim Objection**

At paragraph 5 of the Office Action, claims 92 and 93 are objected to as being of improper dependent form for failing to further limit the subject matter of the previous claim.

Applicants note that claims 92 and 93 have been cancelled, thus making this rejection moot.

In view of the cancellation of these claims, Applicants respectfully request reconsideration and withdrawal of this objection.

## **III. Claim Rejections Under 35 U.S.C. §112**

A. At paragraph 7 of the Office Action, claims 85-93 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner states that claim 85 is indefinite in that a definition of “high stringency” conditions is not included in the claim.

Applicants respectfully note that high stringency conditions are well-known in the art and the skilled artisan is readily aware of the conditions used in a high stringency hybridization experiment. Furthermore, the Examiner's attention is drawn to page 13, lines 4-26, and page 14, line 20 to page 15, line 6 of the specification where hybridization conditions are discussed. Additional written description support for the hybridization conditions can be found in the references cited on page 15, line 5 and lines 15-16, of the specification. As recited on page 55, lines 27-31, all references cited in the specification are expressly incorporated by reference and various modifications can be made without departing from the spirit of the invention.

In view of the full and complete description in the specification of the high stringency conditions recited in the rejected claims, Applicants respectfully assert that the claims are definite as written, and request reconsideration and withdrawal of this rejection.

**B.** At paragraph 8 of the Office Action, claims 86-93 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner states that the rejected claims are unclear because while "substantially pure" is said to exclude other naturally occurring components of CsaE, the subject matter of the claims includes CsaB and the CS4 antigen, thus making the claims inconsistent.

In response, Applicants refer to their comments above under section **I.** and assert that in view of the amendments to claims (use of the transitional phrase "consisting essentially of"), and the statements in the enclosed Declaration Under 37 C.F.R. §1.132 (explaining the inability of CsaE to oligomerize with other proteins encompassed by the claims), each of the claims is definite as currently amended.

In view of the comments above, and the amendments to the claims, Applicants respectfully request reconsideration and withdrawal of this rejection.

C. At paragraph 11 of the Office Action, claims 83 and 85-93 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled.

The Examiner states that claims 83 and 85 encompass homologues of CsaE based on sequence homology (claim 83) and hybridization (claim 85) that are full-length and that are fragments. The Examiner asserts that there is insufficient teachings in the application to enable one in the art to use any homologue or fragment of the claimed invention. Thus, it is the Examiner's position that the genus of polypeptides encompassed by the claims is so large that it is not enabled.

In response, Applicants include herewith amendments to claims 83 and 85 to recite the activity of the homologues (inducing a protective immune response to enterotoxigenic *Escherichia coli*) recited in the claims.

Applicants have also amended the rejected claims such that they encompass only those homologues that are full-length polypeptides or only slightly shorter. The polypeptides encompassed by the claims must have at least 95% homology when compared to the full-length reference sequence. Thus, for a reference polypeptide of 100 amino acids, a homologue could only have a deletion of 5 amino acids to be within the 95% homology requirement.

Thus, the amended claims recited a small genus of polypeptides based on both structural (95% homology over the entire length of the reference sequence) and functional (inducing a protective immune response) features.

In view of this small, well-defined genus of polypeptides, and in view of the teachings in the specification and the knowledge of one of skill in the art, Applicants assert that the skilled artisan would be able to make and use the full scope of the invention as claimed.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

**D.** At paragraph 12 of the Office Action, claims 85-93 are rejected under 35 U.S.C. §112, first paragraph, as being non-enabled.

The Examiner states that while claim 85 reads on CsaE encoded by a polynucleotide that hybridizes to SEQ ID NO:9, it would be the *complement* of the polynucleotide that hybridizes to SEQ ID NO:9.

In response, Applicants include herewith an amendment to claim 85 to address this issue, and assert that the claim is fully enabled as now recited.

In view of the amendment to the claim, Applicants respectfully request reconsideration and withdrawal of this rejection.

#### **IV. Claim Rejections Under 35 U.S.C. §103**

At paragraph 18 of the Office Action, claims 86-93 are rejected under 35 U.S.C. §103(a) as being unpatentable over McConnell in view of Cassels.

The Examiner is maintaining the rejection, as it pertained to claims 12-15 in the previous Office Action, due to the indefiniteness of claims 92 and 93 as discussed above. The Examiner states that as it is unclear whether or not the term “substantially pure” would include the combined antigens of CsaE and CsaB, in view of the open language of the claim (use of ‘comprising’), the claims are being read as including the isolated dimer of the two proteins.

In response, Applicants refer to their comments above in section I. regarding the nature of “substantially free CsaE” and the inability of autonomous combinations of CsaE and CsaB to form an oligomer in the absence of CsaA.

As claim 86 is limited in scope to substantially pure CsaE, and use of the transitional phrase “consisting essentially of”, no other ETEC components which have a material effect on the basic and novel characteristics of the composition are included in the immunogenic composition recited in this claim. As neither McConnell or Cassels, or the combination of the two, teaches or suggests a composition consisting essentially of substantially pure CsaE, the subject matter of claim 86 is not obvious in view of these two citations.

As to new claim 94 (claims 92 and 93 has been cancelled), Applicants refer to the Declaration Under 37 C.F.R. §1.132 enclosed herewith, discussing the relationship between the five Csa polypeptides, and how the CS4 antigen is formed.

As discussed therein, CsaE and CsaB will not spontaneously form the CS4 antigen in the absence of co-factors. Claim 94 does not encompass the co-factor CsaA, in view of the consisting essentially of language in the claims. Thus, CsaE remains in a non-conglomerated form. Because claim 94 recites a composition consisting essentially of substantially pure CsaE, which is not taught or suggested by McConnell or Cassels, these articles also do not teach or suggest the subject matter of claim 94.

In view of these comments and the amendments to the claims, Applicants respectfully assert that none of the rejected claims are obvious in view of McConnell and/or Cassels. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

**V. Requirement for Information**

At paragraph 19 of the Office Action, the Examiner requests information regarding the ability of the CsaE and CsaB proteins to autonomously combine.

In response, Applicants refer to the comments herein and to the Declaration Under 37 C.F.R. §1.132 enclosed herewith, explaining that the CsaE and CsaB proteins do not autonomously combine. Applicants also enclose related journal articles: Sakellaris and Scott, *Mol. Microbiol.* 30(4):681-687 (1998) (cited in the IDS submitted Oct. 4, 2001); Altboum et al., *Infect. Immun.* 71(3):1352-1360 (2003) for the Examiner's review.

**VI. Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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